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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/789,965	ADAMS ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 17-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 17-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 and 17-44 are pending. Applicant has cancelled claim 16. Receipt and consideration of Applicant's amended claims and arguments/remarks is acknowledged.

Specification

The use of the trademark CARBOPOL® [0069] has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-15, and 17-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a method of increasing the amount of a calcium channel blocker delivered to the brain of a patient suffering from hypertension via nasally administering a pharmaceutical composition comprising a therapeutic effective amount of a calcium channel blocker and (2) a method of treating a cardiovascular disease with a calcium channel blocker; wherein both methods utilize a calcium channel blocker selected form verapamil, diltiazem, cinnarizine, and nifedipine, does not reasonably

provide enablement for said methods utilizing all calcium channel blockers known at the time of the invention as well as any new calcium channel blockers which may be developed in the future. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. An analysis of the instant claims utilizing the Wands factors follows.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

The instant claims broadly claim the entire class of chemical compounds called "calcium channel blockers," which is a heterogeneous class of compounds characterized by the attribute of blocking cellular calcium channels. The term "calcium channel" blocker (CCB) encompasses all types of calcium channel blockers that are know as well as any calcium channel blockers that may be developed in the future.

Nature of the invention/State of the Prior Art

The instant inventions are drawn to methods of (1) increasing the amount of CCBs delivered to the brain comprising nasally administering said CCBs and (2) methods of treating a cardiovascular disease with a calcium channel blocker. The prior art recognizes that the pharmaceutical agents classified as CCBs represent a heterogeneous group, in which no common core structure unites all the members of what is considered the group of CCBs. The prior art recognizes that the three primarily prescribed CCBs represent three structural subgroups of known CCBs, wherein prototypical representatives of these are in parentheses: (1) phenylalkylamines (e.g. verapamil), (2) benzothiazepines (e.g. diltiazem), and (3) dihydropyridines (e.g. nifedipine) ((1) Romero, M. et al. "New Advances in the Field of Calcium Channel Antagonists: Cardiovascular Effects and Structure-Activity Relationships," *Curr. Med. Chem. Cardiovascular & Hematological Agents*, **2003**, *1*, 113-141, especially the abstract, pg. 116, right hand column, 3rd paragraph; and (2) Mechanna et al. (U.S. Patent No. 6,951,860), abstract, col. 1, lines 16-30, 55-60; col. 2, lines 16-40). The prior art recognizes three different kinds of voltage-operated calcium channels (VOCs): L-type, T-type, and N-type (Romero et al., abstract, Fig. 4, pg. 115, 2nd paragraph, left column). The CCB structural groups 1-3, described above, and their prototypical representatives have different chemical structures, bind to different receptor sites, and have different pharmacological profiles (pg. 116, right hand column, 3rd paragraph; Table 1 on pg. 117). It is noted that as demonstrated by Mechanna et al. the three structural sub-types described above do not represent all possible CCBs and new CCBs may yet be discovered that comprise structurally different cores from those described above.

Currently, the art recognizes that even a shared core structure is insufficient to enable an artisan to predict the behavior of structurally related CCBs, such as in the case of dihydropyridines (Meredith, P. A. et al. "Dihydropyridine Calcium Channel Blockers: Basic Pharmacologial Similarities but Fundamental Therapeutic Differences," *Journal of Hypertension*, **2004**, *22(9)*, 1641-1648, especially abstract and the 1st paragraph of the section entitled "Clinical Pharmacology"):

> "...Since the fundamental mechanism of action of all CCBs is the same, it might be assumed that findings of these outcome studies can be generalized to all types of CCBs. However, in light of the well-recognized clinical pharmacological differences between 'rate-limiting' agents, verapamil and diltiazem, and the dihydropyridine class of CCBs, this must be considered a misconception...(Meredith et al., abstract)"

The current art also recognizes that Ca^{2+} channels (CCs) are members of a super-family of ion channels that share significant structural and functional homology. The CC family contains ***at least*** 10 members that are distinguished by their structure, subunit composition, location, biophysical properties, and pharmacology, wherein the known CCBs are small molecule ligands for the L-type channel (Triggle, D. J.; "L-Type Calcium Channels," *Current Pharmaceutical Design*, **2006**, *12*, 443-457.) The current art states that ***verapamil and diltiazem are the only therapeutically available members of their respective families*** and that there exists the possibility to develop new drugs that interact with specific subunits of the L-type CC (e.g. gabapentin) (Triggle, pg. 444, right hand column).

Relative Skill in the Art & the Level of Predictability/Unpredictability

The relative skill in the art is high, with ordinary artisans typically having an advanced degree, such as a Ph.D., M.D. Pharm. D., or a combination thereof. It is recognized that the

pharmaceutical arts have an extremely high level of unpredictability. In other words, there is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants have provided working examples in the instant specification, but these are limited to compositions comprising one of the following known CCBs: diltiazem, verapamil, nifedipine, and cinnarizine. Applicant has not taught what structural features are required for a compound to exhibit calcium channel blocking (i.e. antagonist) activity. Although three general structure classes are known in the prior art as corresponding to many known CCBs, the art recognizes that these classes are structurally heterogeneous, but these classes do not represent all known CCBs or provide a predictive ability for the discovery of structurally different CCBs (see Mechanna et al.). Furthermore, it is noted in that the current art recognizes that (1) verapamil and diltiazem are the only therapeutically available members of their respective classes of CCBs; (2) structurally different compounds not belonging to any of the traditionally used CCB classes have been developed (e.g. gabapentin); and (3) new drugs may yet be developed as effective CCBs that bind to specific subunits of the L-type calcium channel (e.g. gabapentin).

For the reasons set forth above, the Examiner concludes that the specification does not reasonably provide enablement for methods of (1) increasing the amount of CCBs (any CCB) delivered to the brain of a patient suffering from hypertension comprising nasally administering said CCBs and (2) methods of treating a cardiovascular disease with a calcium channel blocker (any possible CCB).

The specific claims not discussed above are rejected for depending upon a rejected claim.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant has not described what are the peripherally mediated adverse events that will be minimized upon practice of the method claimed in claim 25. It is noted that the specification mentions the term "peripherally mediated adverse events" in paragraphs [0011] and [0083], but does not elaborate, define, or further describe this term.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-15, 17-26, and 32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it describes a method of "increasing the amount" of a calcium channel blocker delivered to the brain of a patient suffering from hypertension. It is unclear what change Applicant considers sufficient to constitute an increased amount of CCB. Applicant has not provided any standard reference from which to determine what constitutes an increased amount of a delivered CCB. Therefore, a skilled artisan would not be able to ascertain the metes and bounds of the claimed method.

Claims 9 and 32 are indefinite because these utilize the term "purified water." It would be readily recognized by a skilled artisan that there are varying grades and kinds of purified

water. Applicants' have not clearly defined the term "purified water." Therefore, it is unclear what are the intended metes and bounds of the term "purified water" as used by Applicants.

Claim 22 is indefinite because it utilizes the trademark CARBOPOL®. Trademarks are associated with goods and services, which may change at any time based upon the manufacturer's prerogative. Therefore, trademarks are inherently indefinite, when used to refer to a composition of matter. See MPEP § 2173.05 (u).

Claim 25 is vague and indefinite because it is unclear what are "peripherally mediated adverse events" that would be minimized by practice of the method claimed in claim 25. Because the term "peripherally mediated adverse events" is not defined in the specification, a person of ordinary skill in the art would be unable to ascertain the intended metes and bounds of this term as used by Applicants, especially as it relates to administered calcium channel blockers.

The remaining claims are rejected for depending upon a rejected claim.

Claim Rejections - 35 USC § 102

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 1-13, 15, 16, 20-23, 25, 27, 28, 30-36, and 40-42 under 35 U.S.C. 102(b) as being anticipated by Egan et al. (US 2002/0177586) **is withdrawn**, per Applicants' persuasive arguments.

The rejection of claims 1, 2, 5-13, 15, 16, 20-36 and 40-42 under 35 U.S.C. 102(e) as being anticipated by Krause (US 2004/0014782) **is withdrawn**, per Applicants' persuasive arguments.

Claims 1, 3, 5, 8-9, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Fu et al. ("Intranasal Delivery of RS-93522, a Dihydropyridine-Type Calcium Channel Antagonist," Pharmaceutical Research, 1991, 8(1), 134-135).

Applicants claim (1) a method of increasing the amount of a calcium channel blocker (CCB) delivered to the brain of a patient suffering from hypertension via nasally administering a pharmaceutical composition comprising a therapeutic effective amount of a CCB (claim 1), wherein the CCB represents about 0.2% to about 30% by weight of the composition; the composition comprises a pharmaceutically acceptable carrier (claim 3) suitable for nasal drug administration (claim 5); the composition is in the form of a liquid (claim 8); the carrier is purified water, saline, buffer, or a combination thereof (claim 9); the composition further comprises at least one excipient (claim 20) and (2) an improved method of treating a cardiovascular disorder, wherein the improvement comprises nasally administering the CCB.

Fu discloses the **intranasal administration of a CCB-containing solution composition** to anesthetized male Sprague-Dawley rats, wherein the composition comprises **1.0 % RS-93522 (i.e. the CCB), 7% polyoxyethylated vegetable oil (i.e. an excipient), 5% sorbitol (excipient), 0.304% sodium phosphate monobasic monohydrate (buffer), 0.043% sodium phosphate dibasic anhydrous (buffer), and water** for injection qs. to a volume (pg. 134, title; introduction; sections entitled "Composition of Formulation & "Animal Studies", right hand column). Sprague-Dawley rats are art recognized animal models of hypertension. Fu discloses that RS-93522 has been studied **for treating congestive heart failure and hypertension** (pg. 134 introduction).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The rejection of claims 3, 4, 14, 17-19, 37-39, and 43-44 under 35 U.S.C. 103(a) as being unpatentable over Krause (US 2004/0014782) in view of Wermeling et al. (WO 02/13886) is withdrawn, per Applicants' persuasive arguments.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 14-15, 17-20, 23-35, 36-40, and 42-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mechana et al. (U.S. Patent No. 6,951,860) in view of Levin (US 2003/0133877).

Applicant Claims

Applicants claim (1) a method of increasing the amount of a calcium channel blocker (CCB) delivered to the brain of a patient suffering from hypertension via nasally administering a pharmaceutical composition comprising a therapeutic effective amount of a CCB; (2) an improved method of treating a cardiovascular disorder, wherein the improvement comprises nasally administering the CCB; (3) a pharmaceutical composition formulated for nasal drug

administration comprising a calcium channel blocker (CCB) selected from cinnarizine and nifedipine (claim 27), wherein the composition further comprises a carrier (claims 28-29); the composition is a liquid (claim 31) and further comprises at least one excipient (claim 40); and (4) a nasal administrable drug delivery device comprising the composition of claim 28, a means for housing/dispensing unit dosages of the composition into a patient's nasal passage; wherein the device comprises a dry powder inhaler, metered-dose inhaler, medicine dropper, or pump spray bottle (claims 43-44).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Mechanna teaches a family of calcium channel blockers that can be formulated in pharmaceutical carriers and administered to subjects for treating disorders associated with calcium channel activity, including **hypertension, pulmonary hypertension**, migraine disorder, **congestive heart failure, arrhythmia, and angina** (title, abstract, col. 2, line 50 through col. 5, line 14; col. 5, lines 38-56). Hypertension, congestive heart failure, arrhythmia, and angina are all cardiovascular disorders. Mechanna teaches that calcium channel blockers are a chemically diverse class of compounds having important therapeutic value in the control of several cardiovascular disease, including **hypertension, angina, and cardiac arrhythmias** (col. 1, lines 16-22). Mechanna identifies representatives of the three major chemical groups of drugs comprising CCBs: **nifedipine** (dihydropyridines), **verapamil** (phenyl alkyl amines), and **diltiazem** (benzothiazepines) (col. 1, lines 55-58). Mechanna teaches that in one embodiment his invented method includes the step of administering a medicament other than the compound for the treatment of cardiovascular disease, suitable medicaments include **diltiazem malate (for**

hypertension), oxprenolol (a beta-blocker for treating angina), pindolol (a beta-blocker for treating angina), metalazone (diuretic used in the treatment of hypertension), methalthiazide (diuretic used in the treatment of hypertension), methylcyclothiazide (diuretic used in the treatment of hypertension), tasosartan (angeiotensin II receptor blocker used to treat hypertension), eprosartan (angeiotensin II receptor blocker used to treat hypertension), eprosartan mesylate (angeiotensin II receptor blocker used to treat hypertension), enalapril maleate (ACE inhibitor used to treat hypertension), lisinopril (ACE inhibitor used to treat hypertension), peridopril erbumine (ACE inhibitor used to treat hypertension), quinapril hydrochloride (ACE inhibitor used to treat hypertension), and ramipril (ACE inhibitor used to treat hypertension) (col. 6, lines 12-15, 28, 31-33, 38, 43, 45, and 48; col. 7, lines 1, 4-5, 12-13). It is art recognized to deliver drugs from two or more different classes in the treatment of hypertension including beta-antagonists (i.e. beta blockers), ACE inhibitors, CCBs, and thiazide diuretics (*Remington: The Science and Practice of Pharmacy*, Mack Publishing Company: Easton, PA, 1995, pp 943 and 963-966).

Mechanna teaches that an one measure of an effective amount of a pharmaceutical formulation for treating hypertension would be an amount sufficient to reduce the arterial blood pressure so as to achieve a diastolic pressure of approximately 82 mmHg or less and a systolic pressure of approximately 130 mmHg or less (col. 21, lines 57-63) and that generally systemic doses of active agents will be from about 0.01 mg/kg of body weight per day to 10 mg/kg body weight per day (col. 21, lines 65-67). Mechanna's invented **CCBs can be administered alone or with a pharmaceutically acceptable carrier (e.g. lactose)** via a nasal mode of delivery (col. 25, lines 20-23, 30). Lactose is an art recognized solid diluent (i.e. carrier). Compositions

suitable for nasal or bronchial administration include emulsions for aerosol delivery. Aerosols include finely dispersed mist, foam, or **semisolid material**, which is delivered to the nose or mouth as a spray powered by a liquefied or compressed gas or a pump. Aerosols sprays may be **delivered in a pressurized pack or nebulizer with the use of a propellant**, such as fluorocarbon propellants, hydrocarbon propellants, or compressed gases (e.g. nitrogen, nitrous oxide, and carbon dioxide) (col. 26, lines 41-54). Other delivery systems can include **time-release, delayed release or sustained release delivery systems**. Such systems can avoid repeated administrations of the compounds (col. 26, lines 55 through col. 27, line 5). Timed-release, delayed release, and sustained release are all subsets of the genus of controlled release systems (i.e. species of controlled release), per Applicant's admission on page 11 of Applicants' arguments/remarks.

Levin teaches **an apparatus for directed intranasal administration** of a composition comprising a local anesthetic(s) for inhibiting a muscular headache or a cerebral neurovascular disorder (e.g. migraine) (title, abstract, and [0202] through 0204). Levin teaches that headache is a common symptom of numerous disorders and diseases including **severe hypertension** ([0005]). Levin teaches an **intranasal drug delivery device or applicator** ([0069] through [0073], Figures 4A-4L, 5, 6, 7B, and 7C, [0265], [0269], [0274], claims 1-24 and 35). Levin teaches that surface vasodilation effected by an intranasally or dorsonasally administered local anesthetic other than cocaine promotes greater blood vessel recruitment and therefore, greater systemic uptake of the pharmaceutically active agent administered in conjunction with the local anesthetic. Hence, co-administration of a local anesthetic and a pharmaceutically active agent results in a more rapid and greater systemic uptake of the pharmaceutically active agent [0238].

Levin teaches a method of treating a muscular headache comprising co-administration of a CCB (e.g. verapamil) [0245]. Levin's compositions may also comprise an agent that increases or prolongs both the anesthetic effect and tissue uptake of the anesthetic (e.g. permeation enhancer or bioadhesive material) [0248]. Local anesthetics are recognized as having vasodilator activity [0249]. Levin teaches administration of his invented compositions may be affected by providing **a mist or aerosol spray** comprising the composition to the nasal cavity or by introducing into the nasal cavity a **liquid**, gel, semi-solid, **powder**, or foam comprising the composition ([0256], claim 24). Levin teaches that the advantages of intranasal administration are (1) a high local concentration of the composition [0257]; (2) a lesser amount of composition is required than when using different modes of delivery [0258]; (3) enables one to avoid digestive and hepatic metabolism of a drug composition [0258]; (4) self-medication by the intranasal or dorsonasal route is practical [0258]. Levin teaches that suitable devices for intranasal administration of his compositions include **liquid-containing squeeze bottles, pressurized containers, pump-type containers, and droppers**, as well as **microfine powder dispersers and nebulizers** [0269]. **Microfine powder dispersers and nebulizers may be used to deliver powders and atomized liquids, respectively, to the nasal epithelium** and some of the delivered composition may also be inhaled and delivered into the bronchi and lungs, which is acceptable when systemic delivery of a compound is desired ([0274], [0310]).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Mechanna lacks the teaching of a nasal administrable drug delivery device. This deficiency is cured by the teachings of Levin.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Mechanna and Levin, because Mechanna teaches that his compositions may be delivered nasally and Levin teaches a plurality of intranasal delivery devices and apparati. A skilled artisan would have been motivated to combine the teachings of the prior art and modify the compositions of Mechanna to delivery Mechanna's compositions nasally and because Levin teaches that (a) co-administration of a local anesthetic and a pharmaceutically active agent results in a more rapid and greater systemic uptake of the pharmaceutically active agent and (b) that the advantages of intranasal administration include (1) a high local concentration of the delivered composition; (2) a lesser amount of composition is required than when using different modes of delivery; (3) digestive and hepatic metabolism of drugs in the delivered composition is avoided; and (4) self-medication is practical. A person of ordinary skill in the art would have been motivated to combine the prior art teachings because calcium channel blockers are useful for treating migraines, headaches, and hypertension; and headaches are a common symptom of severe hypertension. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings, because Levin's invented devices would enable the nasal administration of Mechanna's compositions and the inclusion of a local anesthetic would promote greater systemic uptake of the active agent co-administered with the anesthetic. The prior art is silent regarding the amount of CCB described

in terms in the weight of the composition administered. This suggests that almost any amount would be suitable in a composition as determined by a skilled artisan through routine experimentation. Applicant needs to demonstrate the criticality of the claimed weight percentages. It would have been obvious to include permeation enhancers in the prior art compositions because these are known in the art as admitted by Applicants (specification, pg. 17, paragraph [0062[) and corroborated by Mahjour et al. (U.S. Patent 5,019,395; col. 4, line 55 through col. 5, line 20).

Claims 21-22 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mechana et al. (U.S. Patent No. 6,951,860) in view of Levin (US 2003/0133877) as applied to claims 1-11, 14-15, 17-20, 23-35, 36-40, and 42-44 above, and further in view of Quay (US 2004/0028613).

Applicant Claims

Applicants claim (1) a method of increasing the amount of a calcium channel blocker (CCB) delivered to the brain of a patient suffering from hypertension via nasally administering a pharmaceutical composition comprising a therapeutic effective amount of a CCB, wherein the composition comprises a bioadhesive material (claim 21) selected from the species listed in claim 22; and (2) a pharmaceutical composition formulated for nasal drug administration comprising a calcium channel blocker (CCB) selected from cinnarizine and nifedipine and comprising a bioadhesive material (claim 41).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Mechanna and Levin have been set forth above. Quay teaches **pharmaceutical formulations** comprising at least one dopamine receptor agonist and **one or more mucosal delivery-enhancing agents**, such as **bioadhesive materials**, **vasodilators** (e.g. **CCBs, ACE inhibitors, angiotensin II receptor antagonists**, etc.) for enhanced mucosal delivery (abstract, [0280]-0283]). Quay states that mucoadhesive compounds include bioadhesive agents, which are used to enhance intranasal delivery of bioactive agents [0348] and a bioadhesive exhibits general or specific adhesion to one or more components or surfaces of mucosal epithelia [0345]. Quay teaches that a variety of suitable bioadhesives are disclosed in art for mucosal administration (see, e.g., U.S. Pat. Nos. 3,972,995; 4,259,314; 4,680,323; 4,740,365; 4,573,996; 4,292,299; 4,715,369; 4,876,092; 4,855,142; 4,250,163; 4,226,848; 4,948,580; U.S. Pat. Reissue No. 33,093; and Robinson, *Proc. Intern. Symp. Control. Rel. Bioact. Mater.* **1991**, *18*, pp 75) [0347]. For example, Tsuk et al. (U. S. Patent No. 3,972,995) identifies as **hydroxypropylcellulose, carboxymethylcellulose, dextran, guar gum, polyvinyl pyrrolidone** and the like as adhesive materials (i.e. bioadhesive materials) for use in buccal dosage forms. Quay also teaches that a bioadhesive in his invented compositions can improve the effectiveness of a treatment by helping maintain the drug concentration between effective and toxic levels, by inhibiting dilution of the drug away from the delivery point, and improving targeting and localization of the drug [0350] and can yield prolonged residence time at the nasal mucosal surface or target site of action of the biologically active agent [0352]. Quay identifies several of the species listed in claim 22 as absorption promoting polymers [0317] (**polyacrylates, polyacrylamides, polyvinylpyrrolidone, and polyvinyl alcohol**), which reads on Quay's definition of a bioadhesive material.

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Mechanna and Levin lack the express teaching of bioadhesive materials. Quay cures this deficiency and is cited herein to demonstrate that bioadhesive materials are well known in the art, especially in the context of compositions intended for nasal delivery.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Mechanna, Levin, and Quay, because the incorporation of bioadhesive materials in compositions intended for intranasal delivery is known in the art. A skilled artisan would have been motivated to modify the compositions of Mechanna and Levin with a bioadhesive agent because Levin teaches the desirability of incorporating an agent that increases or prolongs both the anesthetic effect and tissue uptake of the anesthetic [0248] and Quay teaches that bioadhesive materials can yield prolonged residence time at the nasal mucosal surface or target site of action of the biologically active agent. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings and modification of the compositions of Mechanna and Levin, because the use of bioadhesive materials in an intranasal composition is known in the art and desirable (Levin).

Claims 27-29, 31, 40, and 43-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fu et al. (Pharmaceutical Research, 1991, 8(1), 134-135) in view of Romero et al. (*Curr. Med. Chem. Cardiovascular & Hematological Agents*, 2003, *1*, 113-141).

Applicant Claims

Applicants claim (1) a pharmaceutical composition formulated for nasal drug administration comprising a calcium channel blocker (CCB) selected from cinnarizine and nifedipine (claim 27), wherein the composition further comprises a carrier (claims 28-29); the composition is a liquid (claim 31) and further comprises at least one excipient (claim 40); and (2) a nasal administrable drug delivery device comprising the composition of claim 28, a means for housing/dispensing unit dosages of the composition into a patient's nasal passage; wherein the device comprises a dry powder inhaler, metered-dose inhaler, medicine dropper, or pump spray bottle (claims 43-44).

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Many of the teachings of Fu have been set forth above in the instant office action. Additional teachings by Fu are presented herein. Fu teaches **the intranasal administration of a CCB liquid formulation** comprising delivery of an approximate dose of 35-50 microliter solution of said formulation **into the nostrils of male Sprague-Dawley rats** using a **micropipette** (pg. 134, sections entitled "Composition of Formulation & "Animal Studies", right hand column). A micropipette reads on a medicine dropper. It is noted that the CCB taught by Fu belongs to the dihydropyridine structural class of known CCBs. Romero teaches that

nifedipine is one of the most representative CCBs (abstract) and belongs to the structural class of known CCBs called dihydropyridines (pg. 119, section 2.2, Fig. 6 on page 120, compound 3 in Scheme 8 on pg. 122). Romero teaches that the IV group of the WHO classification includes **cinnarizine**, which **is a diphenylpipierazine calcium channel antagonist** (i.e. a CCB) that exhibits inhibition of contractile processes of the vascular smooth muscle and produces arteriolar vasodilation and peripheral and cerebral vasodilation. (pg. 135, section 2.5 (a) "Diphenylpiperazines"; Fig. 56).

Ascertainment of the Difference Between Scope the Prior Art and the Claims

(MPEP §2141.012)

Fu lacks the teaching of a calcium channel blocker that is nifedipine or cinnarizine. This deficiency is cured by the teachings of Romero.

Finding of Prima Facie Obviousness Rational and Motivation
(MPEP §2142-2143)

It would have been obvious to a person of ordinary skill in the art at the time of the instant invention to combine the teachings of Fu and Romero, because both references identify calcium channel blockers, and Romero reviews the state of the art of calcium channel blocking drugs. It would have been obvious to a skilled artisan to modify the teachings of Fu to utilize either nifedipine or cinnarizine as a CCB, because both nifedipine and cinnarizine are known CCBs (Romero). A skilled artisan would have had a reasonable expectation of success upon modification of Fu's composition to utilize either nifedipine or cinnarizine, because both drugs are known CCBs and have had reasonable expectation of exhibiting calcium channel blocking properties upon incorporation in Fu's compositions.

Double Patenting

It is noted that Applicants' amendments to the instant claims has removed the possibility that if claims 17 and 37 were found allowable, claims 18-19 and 38-39 would be found to be substantial duplicates of claims 17 and 37.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Amer et al. ("Nasal Administration of the Calcium Channel Blocker Diltiazem Decreases Food Intake and Attenuates Weight Gain in Rats," *Pharmacology, Biochemistry, and Behavior*, **October 2005**, *82(2)*, pp 379-387) is cited here for the record, ***but this reference is not prior art***. Amer et al. is relevant because it teaches the nasal administration of a well-known calcium channel blocker (diltiazem).

Claims 1-15 and 17-44 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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